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# Modular Syntheses of Diversonol-Type Tetrahydroxanthone Mycotoxins: Blennolide C (epi-Hemirugulotrosin A) and Analogues

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Among many natural organisms, fungi play a very important, but mostly unexplored role. Their widespread occurrence in soil and marine habitants makes them often a risk but also a challenge for humans. During their lifespan, fungi metabolize and produce a variety of organic compounds, ranging from simple to very complex structures, most of which exhibit certain biological activities. Indeed, some of them are potent toxins, possibly necessary for the self-defense of the fungi. Mycotoxins ("myco" for fungus and toxin)[1] are nonvolatile, relatively low-molecular weight fungal secondary metabolic products that may affect animals such as vertebrates.

Tetrahydroxanthones belong to a larger class of mycotoxins found in many different fungi. Their biological profile ranges from antibiotic to bacterial activities. Prominent members of this group are the well known secalonic acids (**1**; see Figure 1). More recently, a number of new tetrahydroxanthones, such as xanthonol (**2**) or rugulotrosin A (**3**), were isolated from moulds.[2]

Herein, we describe a modular synthesis of tetrahydroxanthones, which allows access to many members of this family.

Despite the fact that they were discovered some 50 years ago and that the Franck group described a hemi-secalonic model nearly 30 years ago,[3] only a few total syntheses of natural tetrahydroxanthenones have been disclosed thus far.

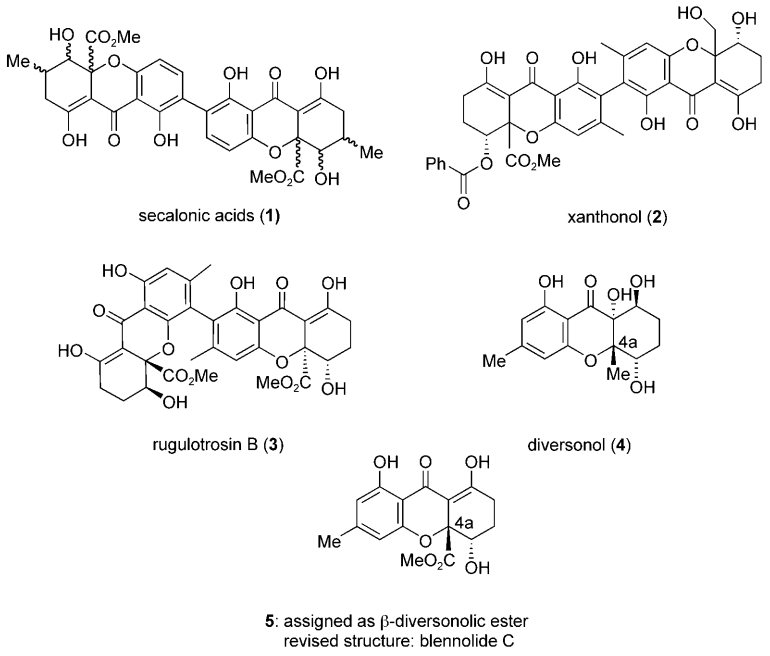


Figure 1. Important tetrahydroxanthone mycotoxins.

The total synthesis of racemic diversonol (**4**) was first achieved by Nising et al.[4] Recently, Nicolaou and Li developed a method to synthesize diversonol (**4**), blennolide C (**5**) as well as α- and β-diversonol esters;[5] Tietze et al. achieved the total synthesis of 4-dehydroxydiversonol.[6]

Nicolaou and Li confirmed the discrepancy between the NMR data and the structure thus assigned of β-diversonolic ester some 30 years ago,[7] which had already been reported

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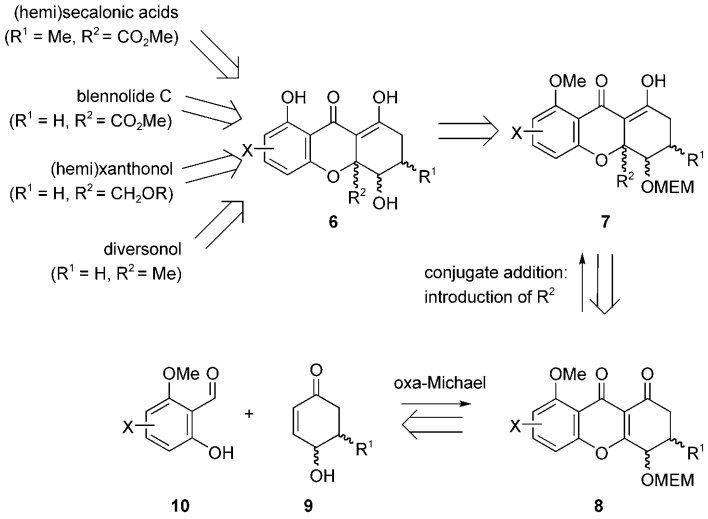
by Krohn and co-workers.[8] Krohn and co-workers were the first to isolate a natural product named blennolide C from *Blennoria sp.*, an endophytic fungus from *Carpobrotus eduli*.[8] Although the NMR data differ from that of β-diversonolic ester, the same structure was assigned to this new compound. Nicolaou and Li confirmed the results by Krohn and co-workers and revised the structure of both diversonolic esters.[5]

Our modular synthesis of substituted tetrahydroxanthones started from unsaturated diketones **8** (Scheme 1). The latter can be obtained in larger quantities via a high yielding sequence including an oxa-Michael–aldol reaction[9] as a key step from aldehydes **10** and cyclohexenones **9**.[10] Building blocks **9** ($R^1$ = H, Me), which are both accessible as enantiomers and in large quantities,[11,12] allow the access to both antipodes of the final natural products.



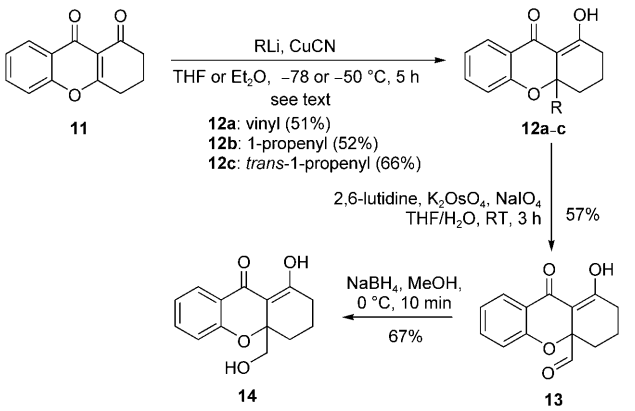

Scheme 1. Modular retrosynthesis of tetrahydroxanthone mycotoxins. MEM = methoxyethoxymethyl.

While diversonol (**4**) has a methyl group at the 4a-position, all other tetrahydroxanthones have higher oxidized functionalities and thus require an acyl anion equivalent (Scheme 1).

With a straightforward access to the model Michael acceptor **11**,[10b] we investigated the key conjugate addition reaction using a variety of reactants (Scheme 2). In the literature, only few articles report on a Michael addition reaction performed on such a sterically hindered skeleton.[13]

To address the oxidation pattern at the 4a-position of rugulotrosin and other mycotoxins, we considered the cuprate addition of an olefin, which can easily be cleaved and therefore gives access to a broad range of natural product analogues.

We were delighted to discover that the use of low or high order cuprates derived from copper(I) cyanide, under optimized conditions, led to the formation of the desired products **12** (Scheme 2).

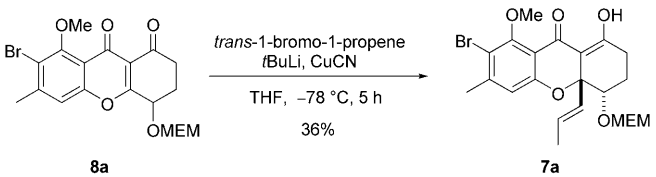



Scheme 2. Synthesis of natural product analogues.

The first substituent to be successfully introduced was a vinyl group. After having evaluated the influence of the equivalents, the order of the cuprate, the temperature, the reaction time as well as the solvent, we were able to reach a yield of 51% using a low order cuprate. However, the formation of the vinyllithium nucleophile required the use of a stannane, which contaminated the product. Since the separation turned out to be quite difficult, we opted for propenyllithium.[14] To our surprise, the high order cuprate this time gave the best results and compound **12b** was obtained in 52% yield (Scheme 2). We also observed that the *cis* reactant was only poorly added to diketone **11**. Thus, we performed the reaction with pure *trans*-1-bromo-1-propene which resulted in a significant improvement of the yield, now reaching 66% for **12c**.[15]

To complete our study on the conjugate addition reaction, we introduced a propenyl group at the 4a-position of a highly substituted xanthone core **8a** (Scheme 3), which has been used for the synthesis of diversonol and has been synthesized using the methodology outlined before (optimized yield over the last four steps for the *cis*-diastereomer: 33%).[4] Under the conditions, optimized on the model system, compound 7**a** was obtained as a single racemic *trans*-diastereomer in moderate yields.[16] This result proved that our method also enables the substitution of complex molecules. Xanthone **7a** is the first synthetic 4-oxyxanthone with an oxidizable C4a-substituent resembling xanthonol (**2**).

Next, our attention turned to the oxidative cleavage of the olefin moiety. We explored the Lemieux–Johnson alternative[17] which was carried out with osmium tetroxide as




Scheme 3. 1,4-Addition reaction performed on a highly substituted xanthone.

catalyst in presence of sodium periodate (Scheme 2). Under standard conditions, only low conversion of olefin **12c** to the corresponding aldehyde **13** was observed even after longer reaction times. As pyridine derivatives are known to accelerate the addition of osmium on a double bond, we used 2,6-lutidine as an additive.[18] Indeed, these conditions afforded the desired aldehyde **13**[19] in 57% yield after 3 h, with minor formation of side products.

With this derivative we were able to synthesize alcohol **14** in good yields by treatment with sodium borohydride in methanol. The resulting reduced xanthones are also present in nature, for example, in natural products such as phomoxanthones, dicerandrols, hirtusneanosides and xanthonol.[2c,20] This approach represents the first successful synthetic route to the dicerandrol half unit. Even though aldehyde **13** could be reduced easily, its oxidation turned out to be quite difficult. In most cases, the oxidation led only to the formation of unstable ketal **15** (10% yield from **13**: $Ca(ClO)_2$, AcOH, MeOH, $CH_3CN$, RT, 1 h) and to unstable ester **16** (18% yield from **13**: KCN, $MnO_2$, MeOH, 0°C, 2 h) (Figure 2). Compound **15** presents the first synthetic approach of the core structure of ergochrom C (**17**), which resembles the monomer of ergoflavin.[21]

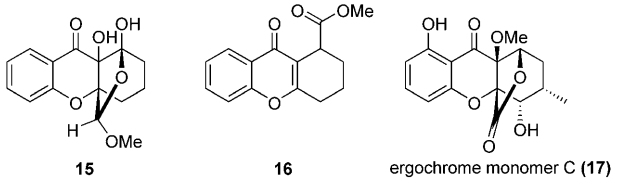
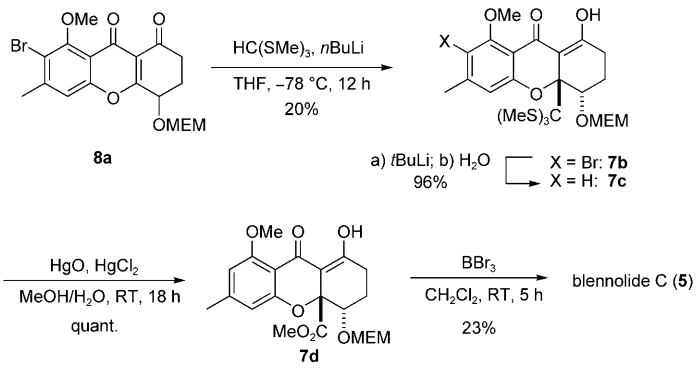



Figure 2. Oxidation products of **13**; ergochrome monomer C (**17**).

For the total synthesis of blennolide C, we used the building block **8a**[4,22] and the Gabbutt method[13b] to introduce the carboxyoxymethyl group (Scheme 4). Hence, reaction of the anion derived from thioorthoformiate gave rise to *trans*-configured diketone **7b**. Removal of the bromine atom,[23] hydrolysis of the *ortho*-thio unit of **7c** into ester **7d** and final deprotection resulted in the isolation of blennolide C. The NMR spectra and analytical data matched perfectly with the data reported by Krohn et al. This result confirms the structure revision of diversonolic ester proposed by Krohn et al.[7] and established by Nicolaou and Li.[5]

A synthetic access to blennolide C opens the route to many other natural products, given that this molecule is also a monomeric part of eumetrin A1, neosartorin and xanthonol (**2**). In addition, the beticolins and xanthoquinodins also include this structural unit.[24]

In summary, we developed an efficient modular synthesis of mycotoxins with functionalities that are frequently found in tetrahydroxanthone natural products. In addition, we were able to convert the compounds into natural products such as blennolide C and desdioxydesmethylhemixanthonol. We continue to study these advanced intermediates and will report on the synthesis of secalonic acids in due course.




Scheme 4. Total synthesis of blennolide C (**5**).

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**Keywords:** aldol reaction · blennolide C · Michael addition · mycotoxins · natural products

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